

TITLE: Can Specific Loading through Exercise Impart Healing or Regeneration of the Intervertebral Disc?

AUTHORS: James Steele BSc (Hons)¹, Stewart Bruce-Low PhD¹, Dave Smith PhD², Neil Osborne PhD³,
Arvid Thorkeldsen DC³

ADDRESS: Centre for Health, Exercise and Sport Science, Southampton Solent University, Hampshire, United
Kingdom¹, Department of Exercise & Sport Science, Manchester Metropolitan University, Cheshire, United
Kingdom², Anglo European College of Chiropractic, Bournemouth, United Kingdom³

CORRESPONDING AUTHOR: James Steele

CORRESPONDING EMAIL: james.steele@solent.ac.uk

CORRESPONDING TELEPHONE: +442380319606

CORRESPONDING ADDRESS: Centre for Health, Exercise and Sport Science, Southampton Solent
University, East Park Terrace, Southampton, Hampshire, United Kingdom, SO14 0YN

CONTRIBUTORSHIP STATEMENT

All listed authors contributions include the conception and design, acquisition of data or analysis and
interpretation of data, drafting the article or revising it critically for important intellectual content, and final
approval of the version published. Regarding responsibility for overall content, the lead author, James Steele, is
the guarantor.

FUNDING

No source of funding was associated with the preparation of this manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

KEY WORDS: Low Back Pain; Resistance Training; MRI

ABSTRACT

Background Context: Low back pain (LBP) is highly prevalent and presents an enormous cost both through direct healthcare and indirectly through significant work and production loss. LBP is acknowledged widely to be a multifactorial pathology with a variety of symptoms, dysfunctions and a number of possible sources of pain. One source that has been suspected and evidenced for some time are the intervertebral discs. Some degree of disc degeneration is a physiologic process associated with aging, however, more severe degeneration and/or structural abnormality may be indicative of a pathological process or injury, and is more commonly present in those suffering from LBP. Much like other tissue's (i.e. muscle, bone etc.) it has been suspected that there exists an optimal loading strategy to promote the health of the disc. Exercise is often prescribed for LBP and effectively reduces pain and disability. However, whether specific loading through exercise might plausibly heal or regenerate the intervertebral discs is unknown.

Purpose: Thus the purpose of this brief review was to examine the effects of loading upon regenerative processes in the intervertebral disc and consider the potential for specific exercise to apply loading to the lumbar spine to produce these effects.

Study Design: A brief narrative literature review

Methods: Studies examining the effects of loading upon the intervertebral discs were reviewed to examine the plausibility of using loading through exercise to induce regeneration or healing of the intervertebral disc.

Results: Research from animal model studies suggests the existence of a dose-response relationship between loading and regenerative processes. Though high loading at high volumes and frequencies might accelerate degeneration or produce disc injury, high loading, yet of low volume and at low frequency appears to induce potentially regenerative mechanisms including improvements in disc proteoglycan content, matrix gene expression, rate of cell apoptosis and improved fluid flow and solute transport.

Conclusions: Research suggests a dose-response relationship between loading and disc regenerative processes and that the loading pattern typically utilised in lumbar extension resistance exercise interventions (high load, low volume, low frequency) might impart healing or regeneration of the intervertebral discs. Future research should examine an exercise intervention with *in vivo* measurement of changes in disc condition. This may provide further evidence for the 'black box' of treatment mechanisms associated with exercise interventions.

Introduction & Background

Low back pain (LBP) is one of the most prevalent medical disorders in society [1-4] and causes significant suffering for many. It presents a cost of billions worldwide (~£5-10 billion UK [5]; ~\$100-200 billion USA [6]), including extensive direct healthcare costs [5-7], and indirect costs through work and production losses (~50-149 million work-days lost [8,9]. LBP is acknowledged as a multifactorial pathology presenting a wide variety of physical symptoms and dysfunctions, some of which may be causative, and others which may be symptoms of underlying dysfunction [10,11].

The intervertebral discs, however, have been suspected to be a potential source of painful symptoms in LBP for some time [12] and there is much well documented supporting evidence regarding mechanisms for how pain may occur [13,14]. Despite the disc being a potential source of pain, in addition to the many biologically plausible mechanisms which might instigate a pain response, there is some disparity in the literature linking the presence of LBP to disc abnormality. Magnetic resonance imaging (MRI) [15-20], radiography [21], and discography [22,23] have all suggested that disc abnormalities can be present in asymptomatic participants, which has brought into question the likelihood of these findings in symptomatic patients holding clinical relevance to the pain they are experiencing. However, recent literature highlights that although it may be difficult to attribute specific disc pathologies to LBP on an individual basis, there are consistent associations of certain disc abnormalities (i.e. high intensity zone (HIZ), degree of disc degeneration, disc herniation and nerve root deviation/compression) in those who suffer from LBP [24-26].

It should be considered also that the subsequent pain response after injury is in part dependent upon severity [27]. In the case of abnormalities in asymptomatic participants it may be that a threshold of degeneration/injury may not have been achieved to initiate a pain causing mechanism. Thus, examination of the literature should consider the severity of degeneration as it relates to LBP. Adams and Roughley [13] suggest the presence of some degree of degeneration is a physiologic process associated with aging, whereas more severe degeneration and/or structural abnormality may be indicative of a pathological process or injury and more commonly present in those suffering from LBP. Many studies support the contention that more severe degrees of degeneration and/or structural abnormality are more consistently apparent in participants with LBP than those who are asymptomatic [16,17,22,23,28] in a dose dependent manner [29,30]. Even if not all disc abnormalities can be ascribed as the source of LBP, any degenerative changes also heighten the risk for more severe disc

degeneration or injury and thus pain and suffering [14]. Thus it seems that, as a consistent finding in symptomatic participants, and a potential source of pain symptoms, disc degeneration or injury is a worthwhile factor to consider in treatment of LBP. Exercise is a common prescription for those with LBP; however, the potential for it to specifically promote positive changes in the intervertebral discs is not often considered.

Loading, Exercise and its Effect on the Disc

Biochemical analysis of the changes involved in symptomatic degenerative discs compared to asymptomatic discs shows that significant metabolic abnormalities are present including; reduced glycosaminoglycans, dehydration, and reduced nucleus pulposus pH [31]. Some have suggested that such metabolic abnormalities in the intervertebral disc might be improved, thus potentially halting or reversing the degenerative process, through appropriate loading of the lumbar spine through exercise [32,33]. However, not all exercises are equally effective in loading and exercising the lumbar spine. A recent review has suggested that the use of isolated lumbar extension (ILEX) may be the most effective exercise for this purpose [34]. Thus it might be considered the most likely candidate for potentially improving disc condition also. Indeed, studies performing ILEX resistance exercise show successful rehabilitation outcomes in terms of pain and disability in participants with diagnosis of degenerative discs [35,36]. In addition, significantly favourable outcomes for participants undergoing lumbar discectomy for disc herniation have been shown as a result of ILEX exercise [37]. Other studies using compound trunk extension training also suggest that the presence of severe disc degeneration at the least has no negative influence on the efficacy of treatment [38].

Despite these findings, there is some opposition to the use of loaded extension based exercise in LBP for fear of causing further damage to the discs [39]. It is suggested that excessive cycles of flexion-extension under a high compressive load may increase the risk of disc herniation [39,40]. The use of ILEX in rehabilitation consists of progressive resistance exercise to train the isolated muscles that extend the lower back [41]. This type of training has been considered therefore to involve increased risk of disk herniation [39]. However the rehabilitation performed typically consists of relatively short times under loading and infrequent training sessions. In contrast, Callaghan and McGill [40] found that the number of flexion-extension cycles was more highly related to disc herniation (upward of 5000 cycles at differing loads). ILEX exercise rehabilitation typically utilises a resistance that will elicit approximately ~8-12 repetitions, and at most around 15 repetitions, before achieving momentary muscular failure using a repetition duration ≥ 7 seconds [41]. Therefore the risk of

1 herniation may not be as great as suggested. There is also concern however that excessive loading may increase
2 rate of disc cell apoptosis [39,42] and may therefore contribute to the inflammatory process by which disc
3 degeneration occurs. However, citing research by Lotz and Chin [42] may be questionable in concluding that
4 excessive loading is responsible for increased apoptosis in this context because the compressive loadings used in
5 this study were applied for periods ranging from 1 to 7 days. In fact, Lotz and Chin's [42] results showed that
6 the degree of apoptosis was proportional to duration of loading; thus longer exposure presented greater risk. As
7 explained, the treatment protocol used with ILEX avoids such sustained loading (through low repetition ranges
8 and frequency of exercise).

9
10 Reviews of the literature suggest the potential for a "safe window" of disc loading to exist that may stimulate
11 optimal disc health [43,44]. Evidence suggesting loaded ILEX exercise as being effective in LBP even when
12 disc degeneration is present has been highlighted [35,36]. Although some studies discussed [40,42] have been
13 interpreted [39] to suggest it could potentially present a risk to the disc, a number of further studies using animal
14 models provide evidence instead for a potential beneficial effect of mechanical loading upon disc degenerative
15 processes, demonstrating biological plausibility for the concept of ILEX resistance exercise for improving disc
16 health.

17
18 Earlier studies have suggested that continued compressive loading can contribute to harmful responses in the
19 disc in a dose-dependent manner (i.e. magnitude and duration), which might further suggest cause for concern in
20 employing ILEX resistance exercise for those with LBP [45,46]. However, this dose-dependent mechanism has
21 important implications for ILEX resistance exercise, which is also typically employed in a dose-dependent
22 manner. As explained, ILEX rehabilitation selects a resistance that allows only ~8-12 repetitions and exercise is
23 performed to momentary muscular failure using this resistance, which has been suggested as optimal for
24 strength and hypertrophic adaptations [47,48]. An exercise frequency of once per week has also been identified
25 as sufficient for improving lumbar extension strength, pain and disability [49,50]. Thus ILEX rehabilitation
26 represents a relatively high loading on the disc though at a low frequency and volume. Walsh and Lotz [51]
27 report that, in comparison to higher frequency and lower load compression, lower frequency and higher load
28 compression induces positive improvements in disc proteoglycan content, matrix gene expression and rate of
29 cell apoptosis. Thus there may be potential for ILEX rehabilitation to exert a similar adaptive effect. Indeed,

Maclean et al. [52,53] have also showed that anabolic and catabolic responses in the nucleus are dependent upon load and frequency with anabolic genes being stimulated at low frequencies and catabolic genes being stimulated at higher frequencies. They also revealed that very low loading had no effect upon gene expression suggesting that some degree of loading, though at a low frequency, is required to stimulate an adaptive anabolic response.

These studies have examined what might be considered regenerative processes, but as we have highlighted, a loss of disc hydration is also present in degenerative discs [31] and so rehydration may also be an important consideration. Ferguson et al. [54] have shown that loading increases fluid flow across the disc, which in turn also enhances transport of larger solutes into the intervertebral disc. ILEX rehabilitation may enhance pressure variance across the disc through its flexion-extension cycles and thus enhance interstitial fluid flow [50]. The findings of Ferguson et al. [54] would lend biological plausibility to this potential mechanism also. A last addition to this discussion of biological plausibility considers the type of loading upon the disc. ILEX typically utilises a dynamic exercise and Wang et al. [55] have presented that while static loading contributes to catabolic activity, dynamic compressive loading contrastingly promotes anabolic activity.

Specific Loading through Exercise May Improve Disc Condition

It is apparent that the intervertebral disc represents a potential source of pain and that disc degeneration is a common factor in LBP. It also seems that ILEX exercise is successful in rehabilitation outcomes even in the presence of such degeneration in symptomatic participants, despite concerns by some authors. As such it seems reasonable to hypothesise that such exercise may in fact impart a healing or perhaps regenerative adaptation to the disc itself. The concept of applied loading in order to promote tissue healing in musculoskeletal conditions (i.e. Mechanotherapy) has been revisited in recent years [56] Indeed as we have discussed, there is significant evidence from animal models to provide biological plausibility for how such an adaptation might occur in the intervertebral discs.

Research has also shown that improvements in both lumbar extensor muscle condition [37,57] and lumbar bone mineral density are produced through ILEX rehabilitation [58-63]. These results might suggest that a sufficient degree of specific loading may be required to promote a positive adaptive response in muscle, bone, and thus potentially the disc also. Indeed epidemiological evidence also suggests that strength training and bodybuilding

1 results in a lowered risk of disc degeneration [64]. Thus we hypothesise that specific loading through ILEX
2 exercise may possibly impart an adaptive response and healing or regeneration of the intervertebral disc.

3
4 It has been suggested that therapeutic pharmacologic interventions could possibly instigate regeneration of the
5 intervertebral disc [65,66] but, despite suggestions for therapeutic loading strategies [43,44,46] the effects of
6 exercise upon disc condition *in vivo* have not been investigated through means of a randomised controlled trial.
7 Adams et al. [14] have recently reviewed the potential for healing to occur in the symptomatic intervertebral
8 disc and suggested that potential mechanisms for disc reparation will likely predominantly involve the annulus.
9 Being that this is an area yet to be examined fully *in vivo*, and that as suggested here there may be mechanisms
10 of positive adaptation in both the annulus and nucleus, we suggest that any study seeking to test this hypothesis
11 should invariably look to examine all possible aspects of disc condition.

12
13 Taken collectively the evidence highlights potential for ILEX exercise rehabilitation to produce beneficial
14 adaptation in the intervertebral discs of symptomatic participants. It also seems apparent that there may be an
15 optimal dose (load, duration, frequency) for which these adaptations are produced. However, these potential
16 adaptations have yet to be investigated *in vivo* through use of MRI. Thus we suggest that in order to test the
17 hypothesis that “specific loading applied through use of ILEX resistance exercise can impart healing or
18 regeneration of the intervertebral disc” be examined through means of a randomised controlled trial to examine
19 *in vivo* changes in disc condition. The intervention used in the trial should follow typical recommendations for
20 ILEX rehabilitation as used in recent studies of ILEX [50,67,68] and could be investigated in both participants
21 with diagnosed disc degeneration and/or injury, in addition to those with non-specific LBP. Ideally the outcome
22 measure used would be MRI and a range of possible factors indicating disc condition be considered for changes
23 using standard validated means of assessment.

24
25 We believe further study of this kind might provide a robust test of this hypothesis and may offer some further
26 insight into the ‘black box’ of mechanisms of exercise interventions effects in LBP [69]. Should the hypothesis
27 be found to be supported then future work might consider comparative studies of interventions, both exercise
28 and other, to examine relative efficacy. However, considering the multifactorial nature of LBP, if an
29 intervention such as ILEX is found to induce positive adaptation in the intervertebral disc this might be

considered as representing further cost effectiveness to the approach due to the wide range of positive outcomes that might be possible from such a minimal single intervention [70].

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